A highly efficient short hairpin RNA potently down-regulates CCR5 expression in systemic lymphoid organs in the hu-BLT mouse model.

Journal: Blood

Publication Year: 2010

Authors: Saki Shimizu, Patrick Hong, Balamurugan Arumugam, Lauren Pokomo, Joshua Boyer, Naoya Koizumi, Panyamol Kittipongdaja, Angela Chen, Greg Bristol, Zoran Galic, Jerome A Zack, Otto Yang, Irvin S Y Chen, Benhur Lee, Dong Sung An

PubMed link: 20018916

Public Summary:

Scientific Abstract:
Inhibiting the expression of the HIV-1 coreceptor CCR5 holds great promise for controlling HIV-1 infection in patients. Here we report stable knockdown of human CCR5 by a short hairpin RNA (shRNA) in a humanized bone marrow/liver/thymus (BLT) mouse model. We delivered a potent shRNA against CCR5 into human fetal liver-derived CD34(+) hematopoietic progenitor/stem cells (HPSCs) by lentiviral vector transduction. We transplanted vector-transduced HPSCs solidified with Matrigel and a thymus segment under the mouse kidney capsule. Vector-transduced autologous CD34(+) cells were subsequently injected in the irradiated mouse, intended to create systemic reconstitution. CCR5 expression was down-regulated in human T cells and monocytes/macrophages in systemic lymphoid tissues, including gut-associated lymphoid tissue, the major site of HIV-1 replication. The shRNA-mediated CCR5 knockdown had no apparent adverse effects on T-cell development as assessed by polyclonal T-cell receptor Vbeta family development and naive/memory T-cell differentiation. CCR5 knockdown in the secondary transplanted mice suggested the potential of long-term hematopoietic reconstitution by the shRNA-transduced HPSCs. CCR5 tropic HIV-1 infection was effectively inhibited in mouse-derived human splenocytes ex vivo. These results demonstrate that lentiviral vector delivery of shRNA into human HPSCs could stably down-regulate CCR5 in systemic lymphoid organs in vivo.